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10/789,008	02/27/2004	Jose Luis Castro Pineiro	T1591	6892
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SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/789,008

Applicant(s)

CASTRO PINEIRO, JOSE LUIS

Examiner

Janet L. Coppins

Art Unit

1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 1-4 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 5-12 and 14 is/are allowed.
- 6) ☒ Claim(s) 13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 1-14 are pending in the instant application.

Election/Restrictions

2. The Markush group set forth in the claims includes both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. For these reasons provided below, restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-4, drawn to methods of claim 1, classified in various subclasses of class 514. A further election of a single disclosed species will be required if this Group is elected.
- II. Claims 10 and 11, drawn to compounds of formula (II) and their compositions, classified in various subclasses of classes 544, 546, 548, 549, or 558. A further election of a single disclosed species will be required if this Group is elected.
- III. Claim 13, drawn to a method of using compounds according to claim 5, classified in various subclasses of class 514. A further election of a single disclosed species will be required if this Group is elected.
- IV. Claim 14, drawn to a process of preparing a compound according to claim 5, classified in various subclasses of classes 544, 546, 548, 549, or 558. A further election of a single disclosed species will be required if this Group is elected.

In addition to an election of one of the above Groups, restriction is further required under 35 U.S.C. 121 as follows:

3. In accordance with the decisions in *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984), restriction of a Markush group is proper where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the other members obvious under 35 U.S.C. 103.

4. Where an election of any one of Groups I-IV is made, an election of a single disclosed compound (in the specification) is further required, including an exact definition of each substituent on the base molecule (formula II), wherein a **single member** at each substituent group or moiety is selected. For example, the base compound has the substituent group Ar¹, wherein Ar¹ is recited to be any of optionally substituted phenyl or heteroaryl, etc., such that Applicant must select a single group and substituent for Ar¹, and each subsequent variable position. In the instant case, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar thereto as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim that fall into the same class and subclass as the elected compound (or set of compounds).

Examination will then proceed on the elected compound AND the entire scope of the invention

Art Unit: 1626

encompassing the elected species, as defined by the above Groups and common classification.

Should applicant traverse on the ground that the compounds are not patentable distinct, applicant should submit evidence now of record showing the compounds to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other.

All compounds falling outside the class(es) and subclass(es) of the selected compound and other compounds encompassed by the elected Group above will be directed to nonelected subject matter and will be withdrawn from consideration under 35 U.S.C. 121 and 37 C.F.R.

1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. (The provisions of 35 U.S.C. 121 apply with regard to double patenting covering divisional applications).

5. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP 608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

6. Each Group listed above is directed to or involves the use of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP 806.04, MPEP 808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over either of the other inventions (Groups), i.e. they are

Art Unit: 1626

patentable over each other. Chemical structures that are similar are presumed to function similarly, whereas chemical that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrefutable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holdings of Applications of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lulu, 223 USPQ 1257 (Fed. Cir, 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other because of the following reasons:

7. Invention II is related to Invention III as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the process as claimed can be practiced with another materially different product since there are other known methods for treating Alzheimer's, including, for example, administering donepezil HCl. Therefore separate search conditions are involved, which would impose a burden if unrestricted.

8. Invention II is related to Invention IV as product made and process of making. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product can be

Art Unit: 1626

made by another materially different process (MPEP 806.05(f)). In the instant case, the product as claimed can be made by another materially different process, please refer to pages 1-2 of the description, wherein Applicants discuss known processes of preparation.

9. The Inventions of Group II are related as mutually exclusive species in the Markush group of formula II. The species are distinct and independent from each other because the compounds differ structurally, one from the other as defined by the different variables recited in the claims. For example, within claim 5, the variable Ar1 alone has many separate, generic possibilities, including, for example, phenyl or any heteroaryl, including pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, oxazolyl, triazolyl, etc, which cannot be said to belong to the same class and subclass of chemical classification. Absent factual evidence to the contrary, each is a different chemical compound.

10. Invention III is distinct and independent from Invention IV because they are directed to different statutory classes of invention and the practice of one of Inventions III or IV would not result in the practice of the other Invention, i.e. treating Alzheimer's is not a process that prepares *per se* a compound of formula II.

11. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Groups II-IV, restriction for examination purposes as indicated is proper.

Advisory of a Rejoinder

12. The following is a recitation of MPEP 821.04, Rejoinder:

Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 809.02(c) and § 821 through § 821.03. However, if

Art Unit: 1626

applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.

Where the application as originally filed discloses the product and the process for making and/or using the product, and only claims directed to the product are presented for examination, when a product claim is found allowable, applicant may present claims directed to the process of making and/or using the patentable product by way of amendment pursuant to 37 CFR 1.121. In view of the rejoinder procedure, and in order to expedite prosecution, applicants are encouraged to present such process claims, preferably as dependent claims, in the application at an early stage of prosecution. Process claims which depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance. Amendments submitted after final rejection are governed by 37 CFR 1.116. Process claims which do not depend from or otherwise include the limitations of the patentable product will be withdrawn from consideration, via an election by original presentation (see MPEP § 821.03). Amendments submitted after allowance are governed by 37 CFR 1.312. Process claims which depend from or otherwise include all the limitations of an allowed product claim and which meet the requirements of 35 U.S.C. 101, 102, 103, and 112 may be entered.

Where product and process claims are presented in a single application and that application qualifies under the transitional restriction practice pursuant to 37 CFR 1.129(b), applicant may either: (A) elect the invention to be searched and examined and pay the fee set forth in 37 CFR 1.17(s) and have the additional inventions searched and examined under 37 CFR 1.129(b)(2); or (B) elect the invention to be searched and examined and not pay the additional fee (37 CFR 1.129(b)(3)). Where no additional fee is paid, if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims which either depend from or include all the limitations of the allowable product will be rejoined. If applicant chooses to pay the fees to have the additional inventions searched and examined pursuant to 37 CFR 1.129(b)(2) even if the product is found allowable, applicant would not be entitled to a refund of the fees paid under 37 CFR 1.129(b) by arguing that the process claims could have been rejoined. 37 CFR 1.26(a) states that "[T]he Commissioner may refund any fee paid by mistake or in excess of that required. A change of purpose after the payment of a fee...will not entitle a party to a refund of such fee..." In this case, the fees paid under 37 CFR 1.129(b) were not paid by mistake nor paid in excess, therefore, applicant would not be entitled to a refund. In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.

13. The following is a recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. 103(b)" (1184 TMOG 86(March 26, 1996)):

"However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all of the limitations of an allowed product claim**. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined." (emphasis added)

Therefore, in accordance with MPEP 821.04 and *In re Ochiai*, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims with process claims commensurate in scope with the allowed product will occur following a finding that the product claims are allowable.

Art Unit: 1626

Until, such time, a restriction between product claims and process claims is deemed proper.

Additionally, in order to retain the right to rejoinder in accordance with the above policy,

Applicant is advised that the process claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

14. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Telephone Election

15. The Examiner thanks Applicants' representative, John C. Todaro, Reg. No. 36,036, for the telephone conversation on March 5, 2007, during which a provisional election was made without traverse to prosecute the invention of Group II, claims 5-12, drawn to compounds and compositions, and the specific compound of Example 2, page 15 of the description. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-4, 13 and 14 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

16. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Status of the Claims

17. Claims 1-12 are pending in the instant application. Claims 1-4, 13 and 14, as previously stated, are withdrawn from further consideration by the Examiner as being drawn to non-elected inventions. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations.

18. After a thorough search, Group II, claims 5-12, appear allowable over the prior art. The restriction requirement between Groups II, III, and IV, as set forth above, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Claims 13 and 14, directed to a method of making and using the compounds of formula II, no longer withdrawn from consideration because the claims requires all the limitations of the allowable product claims. However, Group I, claims 1-4, directed to a different method of use that does not encompass all of the limitations of the product claims, remain withdrawn from consideration because they do not require all the limitations of said allowable claims.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Art Unit: 1626

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971).

See also MPEP § 804.01.

Claim Rejections - 35 USC § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, regarding the treatment of Alzheimer's disease.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

The nature of the invention is the treatment of a subject suffering from Alzheimer's disease.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat

Art Unit: 1626

which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

It is the state of the art that there is no known cure or prevention for Alzheimer's disease, furthermore, there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, ARICEPT®, EXELON®, REMINYL® and COGNEX®, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. MEMANTINE®, which blocks excess amounts of glutamate, treats late stage Alzheimer's disease.

([URL: http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html](http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html)).

The amount of direction or guidance present and the presence or absence of working examples

The only direction and guidance present in the specification is the *in vitro* chemotaxis assay discussed on pages 11-12 of the specification. Applicants have only provided data for one cell line, demonstrating their inhibitory effects on b-amyloid peptide. On pages 2-4 of the

Art Unit: 1626

specification, Applicants cite WO documents that report the role of secretases and NO-releasers in Alzheimer's disease. However, there is no correlation shown between the inhibition of cellular production β -amyloid with treating Alzheimer's disease, i.e. the specification is silent as to the claimed compounds' efficacy for treating any neurodegenerative diseases *in vivo*.

The breadth of the claims and the quantity of experimentation needed

The breadth of the claims is the treatment of Alzheimer's disease. The quantity of experimentation needed is undue experimentation. Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the art would be burdened with undue "experimentation study" to determine whether the claimed compounds not only inhibit the activity of a chemokine, but have efficacy for treating Alzheimer's disease, of which there is no known cure.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and whether Alzheimer's disease would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 5 for the treatment of Alzheimer's disease. As a result necessitating one of skill to perform an exhaustive search for which compounds of the instant claims could be utilized in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 , states that “ a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the *Wands* factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test whether Alzheimer’s disease can be treated by the compound encompassed in the instant claims, with no assurance of success.

Conclusion

21. In conclusion, claims 1-14 are pending, claims 1-4 are currently withdrawn, and claim 13 stands rejected.

Telephone Inquiry

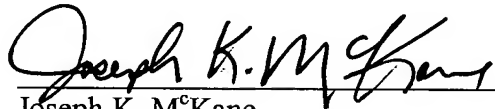
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Coppins whose telephone number is 571.272.0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1626

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Coppins
March 14, 2007



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